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Autoimmune Epilepsy. Literature Review

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SUMMARY
This literature review aims to provide an overview of the current research on autoimmune epilepsy, including its pathophysiology, clinical presentation, diagnosis, and current evidence of therapeutic options. It is based on articles dating from 2002 to 2023. PubMed, Web of Science, Embase, and Cochrane databases were searched to identify relevant articles. The results demonstrate the importance of differentiation between autoimmune-associated epilepsy and acute symptomatic seizures secondary to autoimmune encephalitis to delineate different etiologies, pathogenesis, clinical manifestations, and treatment possibilities. The wide clinical spectrum of disease associated with autoimmune epilepsy includes clinical markers such as extreme delta brush pattern and faciobrachial dystonic seizures that are likely unique to the disease. Autoimmune encephalitis is a mostly treatable disease associated with good outcomes if diagnosis is established early and aggressive immunotherapy is initiated. Autoimmune-associated epilepsy, on the other hand, is a more poorly understood disease that is often treatment-refractory and associated with poorer outcomes.
To conclude, autoimmune epilepsy is a growing field of research in which a better understanding of pathophysiology, more high-level evidence on treatment modalities, increased awareness of the disease, and a wider consensus of terminology are needed to improve clinical outcomes.

KEYWORDS
Autoimmune epilepsy, autoimmune-associated epilepsy, autoimmune encephalitis, symptomatic seizures secondary to autoimmune encephalitis, neuronal antibodies

ABBREVIATIONS

GABA-B	Gamma-aminobutyric acid type B
GABA-A	Gamma-aminobutyric acid type A
NMDA-R	N-methyl-D-aspartate receptor
LGI1	Leucine-rich glioma-inactivated protein 1
CASPR2	Contactin associated protein like 2
GAD 65	Glutamic acid decarboxylase 65
AMPA-R	Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
mGluR5/1	Metabotropic glutamate receptor 5/1
GluR3	Glutamate receptor 3
ANNA-1/Hu	Antineuronal nuclear antibody type 1

CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
EEG	Electroencephalogram
IVIG	Intravenous immunoglobulin G
AED	Antiepileptic drugs

INTRODUCTION

Epilepsy affects 50 million people worldwide. Between 4 and 10 per 1,000 people suffer from active epilepsy with seizures that require active treatment. The World Health Organization estimates that with proper diagnosis and treatment, up to 70% of people affected by epilepsy could be seizure-free (1). However, the low availability of antiepileptic drugs in low- and middle-income countries and a lack of sufficient diagnosis create a treatment gap. Compared to the general population, people with epilepsy have a 2-3% higher mortality rate (2). The majority of deaths worldwide are caused by preventable events such as falls, drowning, burns, and prolonged seizures (1). A diagnosis of active epilepsy is not only associated with higher mortality; it also has a significant social and lifestyle impact on the affected individual. Among them are restrictions on vehicle operation, occupational limitations, social isolation, stigmatization, and discrimination. Unfortunately, in 50% of cases globally, no underlying cause is found, and the etiology remains completely unknown. Therefore, treatment strategies are frequently based primarily on symptomatic control rather than etiology. Epilepsy treatment falls short in approximately 30% of epilepsy cases, which are refractory to medical treatment with anti-epileptic drugs (2). Indicating that there are types of epilepsy that do not respond well to antiepileptic medication. A better understanding of the etiology and pathogenesis in those cases opens up the possibility of reducing the number of cases of drug-resistant epilepsy with new treatment modalities and improved regimens. New treatment strategies could be opportunities to reduce mortality, morbidity, and the burden of disease.

The causes of epilepsy can be generally divided into structural, genetic, infectious, metabolic, immune, and unknown. Among the underdiagnosed and often treatment-refractory types of epilepsy are those with autoimmune causes, which were only relatively recently included in the etiologies section of the most recent International League Against Epilepsy (ILAE) Definition and Classification guideline (3).

In this literature review, the recent major research developments in the field of autoimmune epilepsy will be discussed. The aim of the review is to identify major trends and key issues as well as provide an outlook on the future of research in the field.

METHODOLOGY

The PubMed, Web of Science, Embase, and Cochrane databases were searched to find relevant articles on autoimmune epilepsy initially between the years 2012 and 2023. After the initial search, the publication years were expanded to include publications from 2002 until 2023 to allow a more comprehensive overview. The databases were searched using the following search terms: "autoimmune epilepsy," "autoimmune encephalitis," "limbic encephalitis," "anti-NMDAR," "LGI1," "GABA(B) receptor," "GAD65," "onconeural antibodies," "IVIG," and " The initial search yielded a total of 1,526 articles. Duplicates were deleted, and studies with nonhuman subjects, letters, editorials, and comments were excluded. After screening the titles and abstracts of the results, 238 articles were selected for further screening. After a full-text review, the number of articles included in this review was narrowed down to 50. The choice was limited by the availability of full-text articles through the Vilnius University Library or as free full texts, as well as their availability in English or German.

AUTOIMMUNE EPILEPSY

The term ‘autoimmune epilepsy’ dates back to 2002, when it was first introduced at the International Congress of Autoimmunity in Geneva, Switzerland. It was proposed based on initial findings of glutamate/AMPA Glur3 antibodies in association with Rasmussen encephalitis as well as increasing evidence of epilepsy as a major clinical manifestation of immune-mediated neurological disease such as Hashimoto thyroiditis, multisystem inflammatory disease, and paraneoplastic neurologic disorders. A 2016 retrospective population-based study established that patients with autoimmune disorders have a higher lifetime risk of seizures compared to the general population (4). Initially, the term included any seizure with an autoimmune cause. With the improvement of antibody detection and increased testing for autoimmune causes, the data and publications available have greatly increased. Publications using the term autoimmune epilepsy" have mainly focused on patient cohorts with treatment-refractory seizures with atypical frequency and clinical manifestations. Upon further investigation, the cause of seizures in these cohorts was frequently identified as autoimmune encephalitis (5,6).

With increasing data and a more nuanced body of evidence, it has become apparent that the term "autoimmune epilepsy" is often used too broadly and without clearly defined criteria. In a 2020 paper, the Autoimmunity and Inflammation Taskforce of the ILAE thus suggests using

the terms "acute symptomatic seizures secondary to autoimmune encephalitis" and "autoimmune-associated epilepsy" to differentiate between cases of encephalitis of autoimmune etiology and epilepsy with an autoimmune component in their pathogenesis (7). This differentiation hinges on the classification of epilepsy itself. The definition of epilepsy itself is key to this distinction. Since epilepsy is a condition marked by a persistent propensity to unprovoked seizures, a single seizure is not sufficient for the diagnosis.

One of the major entities that previously fell under the term "autoimmune epilepsy" was identified as autoimmune encephalitis associated with the presence of antibodies in the serum or cerebrospinal fluid (CSF), most commonly targeting neural surface antigens. More than 20% of adult-onset epilepsy with an unknown etiology is caused by autoimmune encephalitis (8). In the acute phase of the disease, autoimmune encephalitis frequently manifests with seizures; however, several other symptoms that are diverse and depend on a specific etiology are also present. Thus, the seizures are only part of the syndrome of encephalitis. These cases tend to respond well to immunotherapy and antiepileptic drugs. With timely treatment, seizure freedom can usually be achieved, and antiepileptic medication can eventually be discontinued. Due to the temporality and treatability of the seizures, the taskforce suggests that the use of the term epilepsy in these cases is no longer appropriate and may even be harmful due to the restrictions that are associated with the diagnosis of epilepsy. Instead, they introduce "acute symptomatic seizures secondary to autoimmune encephalitis" as a more appropriate descriptor of the condition (7).

The remaining patients who have chronic immune-mediated seizures are assigned the term "autoimmune-associated epilepsy." They present with chronic seizures, the presence of antibodies targeting intracellular antigens such as GAD56 and onconeural protein antibodies, or Rasmussen syndrome. The inflammatory changes in these cases are thought to be mediated by cytotoxic T-cells, with the antibodies occurring as an epiphenomenon of the inflammatory response (9). Structural change has been documented as an underlying cause of these seizures in some cases (10). Immunotherapy as well as anti-seizure medication are often ineffective. Leading to the persistence of the predisposition to seizures and a resulting chronic course of epilepsy. In these cases, the defining criteria of epilepsy, where there is a disturbance in the brain that leads to a constant seizure predisposition, are fulfilled. Consequently, the use of the term "epilepsy" is appropriate. There are cases in which autoimmune encephalitis becomes chronic and evolves into epilepsy. This has been documented with both surface antibodies (11)

and intracellular antibodies (12). It is hypothesized that this is the result of either ongoing active immune-mediated inflammatory processes or acute encephalitis-associated immune-mediated structural brain injury (13).

PATHOPHYSIOLOGY

The discovery of neural-specific antibodies has led to significant advances in our understanding of pathogenesis, including the variety of pathologic mechanisms that underly these syndromes.

An underlying occult tumor serves as the immunological trigger in paraneoplastic entities. Because the tumor cells express an onconeural antigen, the immune system reacts inappropriately to it, which ultimately causes neuronal dysfunction. In some cases, the antibodies are tumor-specific, like antineuronal nuclear antibody type 1 for small cell lung carcinoma and Ma-2 for testicular germ cell cancer (14). Autoantibodies against intracellular autoantigens such as antigen Ma-2, Hu, or CV2/CRMP5 are surrogate biomarkers. The neuronal injury in these cases is attributed to a CD8+ cytotoxic T-cell response, which may share the same autoantigen specificity. The autoantibodies themselves do not have a direct action on neuronal injury (15,16).

Another potential trigger for autoimmune neurological syndromes such as autoimmune encephalitis and epilepsy are infections, such as herpes simplex virus encephalitis, which is associated with NMDA-R encephalitis (17). Proposed pathogenic mechanisms include molecular mimicry, epitope spreading, and bystander activation (18). Structural and amino acid sequence similarities may lead to a cross-reactive immune response. Cellular damage caused by the infection may lead to autoantigen release, which triggers an autoimmune response. Alternatively, the infection may lead to the activation of autoreactive lymphocytes and antigen-presenting cells, which then mediate a response to autoantigens.

Some surface epitopes have a direct pathogenic role, such as LGI1 and NMDA-R. Anti-LGI1 has been speculated to cause its pathogenic effect through ion channel deficiency, disrupting calcium influx (19). NMDA-R antibodies disrupt the interaction between the NMDA receptor and the ephrin type B2 receptor, which ultimately leads to the internalization of the NMDA receptor, contributing to neuronal dysfunction (20,21).

The neuronal damage in GAD65 antibody-associated epilepsy is considered to be brought on by cytotoxic T cells, which release perforin and a number of granzymes and cause the

GABAergic interneurons to malfunction. It has been hypothesized that the immunological reaction to GAD causes an inhibition of its function, which results in a reduced conversion of glutamate to GABA. It lowers the seizure threshold by causing an overabundance of excitatory neurotransmitters and a lack of inhibitory action (22,23).

CLINICAL PRESENTATION AND DIAGNOSTIC FEATURES

Since 1965, twenty-six distinct autoantibodies have been found in individuals suffering from intractable epilepsy or encephalitis with seizures. The disease entities brought on by these autoantibodies have a wide spectrum of manifestations, including limbic encephalitis, cerebellar degeneration, brainstem encephalitis, and encephalomyelitis. The most commonly identified neural-specific antibodies are LGI1, NMDA-R, and GAD65. The spectrum of clinical presentations for the more commonly identified antibodies and those who most frequently present with seizures as part of their syndrome has been included in the following.

Anti-NMDA receptor encephalitis is caused by antibodies against the NR1 subunit of the NMDA receptor, which have been identified in the cerebrospinal fluid. Clinically, it manifests with a prodromal period, which may last several weeks and manifest with symptoms like fever, headache, nausea, vomiting, and diarrhea. The prodrome is followed by the symptomatic phase, which presents with psychiatric and behavioral symptoms. Among them are anxiety, bizarre behavior, delirium, paranoia, insomnia or hypersomnia, and an altered level of consciousness. In the symptomatic phase, focal or generalized seizures, autonomic instability, and hypoventilation can occur. Additionally, patients can present with movement disorders such as oral-motor dyskinesias and choreiform movements (24). The diagnosis is supported by the identification of NMDA receptor antibodies in the cerebrospinal fluid; the serum may be negative for antibodies in these patients. Cerebrospinal fluid analyses may also show lymphocytic pleocytosis, elevated protein levels, and positivity for oligoclonal bands. Brain magnetic resonance imaging (MRI) is abnormal in only approximately half of cases in which cortical or subcortical FLAIR signal hyperintensities have been observed. The electroencephalogram (EEG) is abnormal in most patients but usually non-specific. Possible findings include diffuse slowing and an extreme delta brush (EBD) pattern occurring in up to approximately 31% of patients (24, 25). EBD pattern has been suggested as a predictor for severe disease course and occurrence of status epilepticus in two studies from 2012 and 2015 (27,28). Association of EBD with status epilepticus could not be confirmed in follow up

studies; however, further evidence of EBD as a marker for severe disease and worse short-term outcomes was found (29,30).

Two voltage-gated potassium channel antibodies have been identified in association with limbic encephalitis: antibodies against the leucine-rich glioma inactivated protein 1 (LGI-1) and against the contactin-associated protein 2 (CASPR-2). Limbic encephalitis manifests as short-term memory loss, intractable focal seizures with high frequency and commonly with temporal lobe features, hyponatremia, dysautonomia, sleep disturbance, and psychiatric symptoms. Focal sensory olfactory seizures or focal autonomic seizures with piloerection are two distinctive seizure types that may occur in limbic encephalitis. Paroxysmal dizziness spells are uncommon but characteristic of LGI1-antibody encephalitis (7). Faciobrachial dystonic seizures can precede limbic encephalitis in patients with LGI1 antibodies and manifest as brief dystonic seizures that mainly affect the arm and ipsilateral face (31). The diagnosis of VGKC-associated limbic encephalitis is based on the presence of either anti-LGI1 or anti-CASPR2 in the serum. Usually, no abnormalities are seen in the cerebrospinal fluid. MRI often shows mesial temporal T2 hyperintensity, usually asymmetric and non-enhancing, but it can also be normal. Frontotemporal general slowing and focal temporal epileptiform discharges may be seen on the EEG (32).

Limbic encephalitis as described above is also associated with GAD65 antibodies, GABA(B)-receptor antibodies, and AMPA-R antibodies. Anti-AMPA-R limbic encephalitis and Anti-GABA(B)-R encephalitis are diagnosed with the detection of the antibody in the serum. AMPA-R encephalitis it is most commonly seen in older patients in association with cancers of the thymus, breast, or lung. These patients should therefore be screened for those types of cancer. Anti-GABA(B)-R associated limbic encephalitis cases are mostly found in adults with small lung cell carcinoma (33).

GABA(A) receptor antibody has been associated with encephalopathy manifesting with crescendo seizures and often refractory status epilepticus. CSF findings are often abnormal, and brain MRI shows multifocal cortical and subcortical hyperintensity. 10–30% of cases are associated with thymoma.

Paraneoplastic antibodies such as Hu, Ma2, Cv2/CRMP-5, and mGluR5 have some commonalities in their clinical manifestation. They present either as isolated limbic encephalitis or with more widespread signs of nervous system involvement like peripheral neuropathy, cerebellar degeneration, brainstem encephalitis, and autonomic dysfunction.

Abnormal CSF findings are seen in approximately 70% of cases; MRI shows mesial, temporal, or diffuse changes. In over 50% of cases, the diagnosis of paraneoplastic limbic encephalitis precedes the diagnosis of cancer. All patients should be screened for occult malignancy (35).

GAD65 antibodies have been associated with both acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy. The first presents with an acute onset of seizures with or without cognitive and psychiatric disturbances, including amnesia and encephalopathy. In these cases, the first seizure manifestation may be new-onset refractory status epilepticus, and patients show MRI evidence of limbic encephalitis (34). Younger individuals are more commonly affected, and the seizures are less likely to respond to antiepileptic drugs (AEDs). In GAD65 antibody-associated limbic encephalitis, titers above 20 nmol/l in the serum are associated with neurological symptoms. The diagnosis is based on identification in the cerebrospinal fluid (12). The other possible presentationof GAD65 mediated disease is chronic treatment refractory epilepsy without evidence of active CNS inflammation clinically or on the MRI scan.

In autoimmune-associated epilepsy without definitive features of encephalitis, diagnosis is much more challenging since suspicion of autoimmune etiology often only arises very late in the process. Seizures are often the only presenting symptom. It is mainly mediated by intracellular antigens, which are frequently paraneoplastic; the exception is GAD65-related epilepsy. Since the antigens are intracellular, cytotoxic T lymphocytes are suspected to be the cause of the pathology and have been found in histological preparations of postsurgical brain tissue samples in patients with drug-resistant epilepsy (36).

Rasmussen syndrome is an uncommon disorder characterized by refractory seizures, progressive cortical atrophy, and neurologic impairment. The median age of onset is six years of age, with only 10% of cases occurring in adults. It is an outlier in the spectrum of autoimmune-associated seizures since the syndrome is well described, but the exact cause remains unknown. Specific autoantibodies have not yet been identified in association with Rasmussen syndrome. Initially, GluR3 was suspected as the origin of the disease, but it has since been proven to be nonspecific for the disease. More recent studies indicate that T-cell-mediated inflammation leading to lymphocyte infiltration, microglial activation, gliosis, and ultimate neuronal loss in the affected hemisphere plays a role in the pathophysiology. Patients present with focal motor seizures that progress over time in both frequency and severity. The

seizures may evolve from focal to bilateral tonic-clonic seizures or epilepsia partialis continua, which are recurrent focal motor seizures that occur every few seconds or minutes for extended periods (from days to years). Prior to seizure onset, patients may experience unilateral limb dystonia or choreoathetosis. Over time, progressive hemiparesis develops. Late-onset cases have been shown to progress more slowly. The diagnosis is based on clinical presentation and the demonstration of progressive hemispheric atrophy on neuroimaging. CSF may be normal or show mild pleocytosis, mildly elevated protein, and oligoclonal bands. Hemispheric slowing and epileptiform abnormalities can be seen on the EEG (37).

In 2016, Graus et al. proposed a diagnostic algorithm to improve the clinical approach to autoimmune encephalitis (38), which focused on improving the diagnostic approach using neurological assessment and testing with MRIs and EEGs that is accessible for most clinicians to improve the speed at which the diagnosis of an autoimmune cause of epilepsy is made. In 2019, Dubey et al. proposed the "antibody prevalence in epilepsy and encephalopathy score' (APE^2) as a clinical tool for systematic identification of autoimmune encephalitis or autoimmune-associated epilepsy. It considers the rapid onset of symptoms, the presence of neuropsychiatric changes, autonomic dysfunction, viral prodrome, faciobrachial dystonic seizures, facial dyskinesias, intractable seizures, CSF findings consistent with inflammation, brain MRI suggesting encephalitis, and the diagnosis of systemic cancer within 5 years of neurological symptom onset. The presence of each of the mentioned categories is assigned a numerical value between one and three. The total achievable score is 18. A score of 4 or greater was shown to be 99% sensitive and 94% specific for neural-specific antibodies (39).

TREATMENT

Usually, in patients presenting with recurring seizures, treatment is pharmacotherapy with antiepileptic drugs for seizure prevention. In autoimmune epilepsy, the overall efficacy of antiepileptic drugs was estimated to be only 10.7% in a systematic review by Cabezudo-García et al. They found that seronegative patients and patients refractory to immunotherapy were more likely to respond to AEDs; VGKC-positive patients were least likely to respond (40). When discussing the treatment for autoimmune epilepsy, it is once again important to differentiate between seizures that occur as an acute presentation of autoimmune encephalitis and autoimmune-associated epilepsy.

Since AEDs show limited efficacy, treatment approaches for autoimmune encephalitis are instead focused on targeting the cause. The goal is to reduce the immune response and inflammation, enhance GABAergic activity, and achieve seizure and symptomatic control. To achieve these goals, a range of immunomodulatory treatments and AEDs have been used. The established treatment regimens consist of first-line and second-line immunotherapy. First-line therapy includes intravenous corticosteroids (mainly methylprednisolone), intravenous immunoglobulins, and plasmapheresis. Second-line treatment options are more aggressive, such as rituximab and lymphocyte antiproliferative agents such as cyclophosphamide, mycophenolate mofetil, and azathioprine.

Early initiation of the treatment has been shown to correlate with better patient outcomes by Graus et al. (2016) (38).

A Dutch cohort study from 2019 evaluated seizure treatment for anti-LGI1, anti-NMDAR, and anti-GABA(B)R encephalitis. It included 153 patients who experienced epileptic seizures and tested positive for one of the three antibodies, which were treated with AEDs and immunotherapy. First-line immunotherapy was used in 92% of patients; 17% additionally received second-line immunotherapy; and 80% of patients received AEDs. In 89% of patients, seizure freedom was achieved; of those, 14% achieved seizure freedom with only AEDs, 53% became seizure-free shortly after initiation of immunotherapy, and 68% achieved seizure freedom with a combined treatment of immunotherapy and AEDs. Overall, they showed that there is a higher chance of achieving seizure freedom with the use of immunotherapy (11).

Several other studies including Titulaer et al. (41), van Sonderen et al. (42), Ariño et al. (43) and Höftberger et al. (44) have further established the efficacy of first and second line treatments in autoimmune encephalitis. The results of these studies are detailed below in Table 1.

Table 1.

Study	Titulaer et al.	van Sonderen et al.	Ariño et al.	Höftberger et al.	De Bruijn et al.
Detected Antibodies	NMDAR	CASPR2	LGI-1	GABA B R	LGI-1, NMDAR, GABA(B)R
Main clinical manifestations	Anti-NMDAR Encephalitis, seizures	Limbic encephalitis, seizures	Limbic encephalitis, seizures	Limbic encephalitis, seizures	Limbic encephalitis, seizures, panencephalitis
Number of patients receiving treatment	501	30	48	19	110
1st line treatment	462	28	48	15	101
Corticosteroids	421	16	26	14	97
IVIG	346	13	0	7	60
Plasma exchange	163	3	7	5	7
Second line treatment	134	7	6	3	17
Rituximab	101	5	3	2	16
Cyclophosphamide	81	2	7	1	7
Other	31	1	1	1	/
Outcome	mRS 0-2: 394 mRS 3-5: 77 mRS: 6	mRS 0-2: 24 mRS 3-5: 5 mRS 6: 4	CSP0-1 34 (71%), CSP2-4 (29%)	complete treatment response 44%, partial response 50%, no response 6%, death 40%	Seizure freedom: 98 (89%)
Relapse	45	7	10	No data	25

The outcomes were measured based on the modified rankin scale (mRS) for neurologic disability, the cognitive performance scale (CSP) (see Appendix), completeness of response to treatment, and seizure freedom. Especially Titulaer et al. provide significant evidence that in patients with anti-NMDA receptor encephalitis who do not respond to first-line therapy, second-line therapy is usually successful.

In patients with high antibody titers, plasma exchange may be especially effective, as shown in a 2019 Chinese study (45). Whereas IVIG has been demonstrated to be less effective in autoimmune encephalitis caused by intracellular antigens (46). Instead, cyclophosphamide might be considered a first choice, according to an observational study from 2018 by Macher et al. (47).

A 2021 multicenter study examined the use of rituximab in autoimmune encephalitis treatment. The study included 358 patients with NMDAR-, LGI1-, CASPR2-, and GAD65-associated diseases. In patients with NMDAR autoimmune encephalitis, rituximab treatment was associated with better long-term outcomes; in LGI1 autoimmune encephalitis, no significant difference in clinical improvement was seen compared to other treatment regimens. In CASPR2 antibody-positive patients, only rituximab treatment showed clinical improvement. And no improvement was seen in GAD65 antibody-positive patients. They also show a significant reduction in the relapse rate for rituximab-treated patients from 13% to 5%. Early treatment initiation was associated with a more favorable outcome for those entities responding to rituximab (48).

The poor responsiveness of anti-GAD65 antibody-mediated disease to immunotherapy has also been described in a 2018 article summarizing case reports and smaller studies on GAD65-associated epilepsy. The article describes the potential of early identification to

reduce chronic seizure burden when long-term aggressive immunosuppressive therapy with Rituximab, cyclophosphamide, or mycophenolate mofetil is started. However, even then, mostly moderate to poor responses were seen, with a much worse response and long-term outcome compared to autoimmune encephalitis with acute seizures (22).
Besides etiologic treatment, symptomatic treatment with AEDs may be useful. Up until now, there has been no conclusive data on which AED is the best choice when treating acute symptomatic seizures in autoimmune encephalitis. De Bruijn et al. document evidence that in cases of anti-LGI1 autoimmune encephalitis, carbamazepine produces better seizure control than levetiracetam (11).

Ilyas-Feldmann et al. determined the long-term seizure outcome in patients with autoimmune encephalitis, analyzing relapse rates and the safety of AED discontinuation. The results showed that in seizure-free patients, AEDs can be safely withdrawn without any relapse of seizures (49). If a relapse occurs, long-term immunosuppression may be indicated, according to Abboud et al. (50). Medication options include azathioprine, mycophenolate mofetil, and rituximab, and treatment may be indicated for up to two years.

Evidence for autoimmune associated epilepsy treatment is scarce. Since the disease entity is not yet well described, there is very limited data on therapy options. In a trial by Toledano et al., out of 110 patients screened, 29 met the criteria for "suspected autoimmune epilepsy" and were started on a 6- to 12-week trial of intravenous corticosteroids, IVIG, or both. They found that 62% of patients had a reduction of more than 49% in seizure frequency (51).

A 2017 retrospective study examined the efficacy of epilepsy surgery as a possible treatment option for drug-resistant epilepsy associated with neuronal antibodies. Mar Carreño et al. found that in a cohort of patients with GAD, Ma2, Hu, LGI1, and CASPR2 antibodies, the majority of whom underwent anteromedial temporal lobectomy, 38.4% were seizure-free or almost seizure-free upon follow-up; 23% saw no worthwhile improvement (36).
In the treatment of Rasmussen syndrome AEDs have been shown to be ineffective (37). There is evidence that some patients improve with corticosteroids, IVIG, plasma exchange, tacrolimus, and azathioprine (52–54). In children most effective therapy still seems to be functional hemispherectomy, however it is a radical treatment option which comes with severe sequelae. When performed in infancy it is believed that the high plasticity of the infant brain can lessen the severe consequences (55).

Alongside the APE^2 score for the diagnosis of autoimmune epilepsy, the Response to Immunotherapy in Epilepsy score was developed and validated based on retrospective data by Dubey et al. in 2017. It includes the same criteria as the APE^2 score with two additional criteria: initiation of immunotherapy within six months of symptom onset and detection of neural plasma membrane autoantibodies. The maximum achievable score is 19. The aim of the score is to simplify the decision to initiate immunotherapy, especially in cases with negative or nonspecific neural antibody results. They showed that a RITE^2 equal to or greater than 7 predicted a favorable outcome of immunotherapy with 87.5% sensitivity and 83.8% specificity, thus providing an objective guideline on the usefulness of immunotherapy initiation (56).

DISCUSSION

The proposed new definition and terminology by the ILAE taskforce for differentiating between them is relatively recent and has only been used in a few recent publications. Before the recommendation for the use of terminology like "autoimmune epilepsy," "autoimmune encephalitis" was less clearly defined. This led to confusion and a certain degree of opacity, which slowed the research process significantly. Wider implementation of the new terminology could improve future publications since the basis of the clinical studies, such as inclusion criteria and treatment regimens for specific diseases, might become less heterogeneous, more transparent and easily comparable.

Across the board, it was difficult to find studies with a high level of evidence. The majority of studies were retrospective cohort studies and case series, with a few prospective observational studies and clinical trials. There were no double-blinded randomized controlled trials at all. In 2019, a randomized placebo-controlled trial was attempted to investigate the efficacy of IVIG in LGI1/CASPR2 epilepsy, but it was stopped due to slow enrollment. which may be a good example for a possible explanation of the current low level of evidence: the diseases are rare, and thus, finding enough suitable patients is difficult. The LEGIONE study is a currently enrolling randomized, double-blind, placebo-controlled study that aims to evaluate the safety of rozanolixizumab in patients with LGI1-autoimmune encephalitis and will become the first RCT in the field if successful.

Significant advancements have been made in understanding the pathophysiology of autoimmune encephalitis; however, when it comes to autoimmune-associated epilepsy, Rasmussen syndrome, and many of the newly recognized autoantibody-associated

encephalitides, the pathophysiology still remains largely a mystery. Further investigation could shed some light on issues encountered in the clinical setting. With the increased recognition of causative autoantibodies the diagnosis and understanding of autoimmune encephalitis has improved greatly, however further research into autoantibodies and their role as biomarkers in diagnosis, prediction of severity and treatment response are areas could lead to improvement therapy and outcomes.

Analyzing the clinical manifestations highlighted the wide spectrum of presentations. At the same time, there is significant overlap between the different antibody-associated autoimmune encephalitis and epilepsies. In general, autoimmune encephalitis with acute seizure syndrome presents with the onset of symptoms within a few days or weeks. A viral-like prodrome with symptoms like headache and hyperthermia can lead to an initial suspicion of a viral or bacterial cause. New-onset intractable seizures and altered memory, behavior, and mood occur in most autoimmune encephalitides. Which symptoms predominate, their severity, and the presence of other features such as faciobrachial dystonic seizures, hyponatremia, or dyskinesias allow for differentiation between the types of autoimmune encephalitis. A facio-brachial dystonic seizure may be unique to LGI1 encephalitis and play an important role in its early detection. With the help of magnetic resonance imaging, the diagnosis can be narrowed down further; it is especially helpful in limbic encephalitides and Rasmussen syndrome. EEG is almost always abnormal, but only the extreme delta brush pattern may be pathognomic for anti-NMDAR encephalitis. A normal EEG does not rule out the diagnosis.

Autoimmune associated epilepsy on the other hand is less well described. Its main and often only clinical presentation are seizures which can vary from focal to new-onset refractory status epilepticus.

The overlap in clinical presentation, the rare occurrence of the disease, and a lack of awareness all contribute to a complicated differential diagnosis and a possible delay in diagnosis. Which is especially detrimental since one of the most well-established ways to improve disease outcome is early diagnosis and appropriate, intense treatment initiation. Possible improvements in differentiation and especially early detection can be made with the APE2 score, which, due to its high specificity and sensitivity, seems like a promising tool. It represents the only objective diagnostic score thus far and is quick and easy to apply. It also addresses the issue that, in practice, it is not feasible to test every patient with suspicion of encephalitis or with intractable seizures for all neural-specific antibodies. Especially newly discovered antibody testing is likely not available in most laboratories. The score could be an important tool to improve cost-effectiveness by narrowing down patients who should be

tested for autoantibodies. The validity of the score could be further cemented with supporting data from clinicians implementing it in their practice. A limitation to its use could be its lack of distinction between autoimmune encephalitis with acute seizures and autoimmune-associated epilepsy.

Treatment for autoimmune encephalitis is well established. The most important principles of treatment are the importance of establishing autoimmune etiology as early as possible, inducing high intensity immunotherapy early on and adding on AEDs for symptomatic control if necessary. Good efficacy of first- and second line immunotherapy has been demonstrated, but there is still a significant proportion of patients who do not respond to treatment. Furthermore, more data is needed on the dosing regimens and which of the first-line treatment options should be used first, and timing of second-line therapy. There are some current suggestions but they are based on observational evidence and expert opinions. Implementation of the RITE^2 score as a tool for prediction of favorable outcome with initiation of immunotherapy could be especially useful for clinicians unfamiliar with the disease entities.

CONCLUSION

The topic of autoimmune epilepsy is a rapidly growing research field in neurology. The importance of distinguishing between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy has been highlighted, especially in regards to starting appropriate treatment at the appropriate time. A wider consensus on terminology use could also improve transparency and understanding in the field.

There are still many open questions in the pathophysiology of both autoimmune-associated epilepsy and autoimmune encephalitis. Improving the understanding of pathophysiology could lead to new treatment approaches, especially for treatment-refractory entities such as GAD65-associated disease, Rasmussen syndrome, and chronic autoimmune epilepsy. Clinical manifestations can be variable and difficult to distinguish, but significant steps towards diagnosis can be made with widely available diagnostics such as EEGs and brain MRI, especially in regards to distinctive features such as extreme delta brush patterns and facio-brachio dystonic seizures.

In the future, with wider implementation of the APE^2 and RITE^2 scores, their usefulness could be confirmed and early diagnosis and treatment initiation could be simplified. With early aggressive treatment, full recovery with few relapses is achievable for acute symptomatic seizures following autoimmune encephalitis. Long-term AED treatment or

restrictions on daily living are not necessary with successful treatment. For autoimmune encephalitis treatment consists of first-line immunotherapy with corticosteroids, IVIG, and plasma exchange. If first-line treatment fails, second-line treatment with rituximab and cyclophosphamide shows improvement in most patients. Some patients remain refractory to both first- and second-line treatments. For autoimmune associated epilepsy there is a general lack of data, and now standardized treatment regimen is supported by the current evidence. Autoimmune modulatory therapy, AEDs and surgery are among the described treatment options with some rates of success.

The rarity of the syndromes makes the establishment of a high-level evidence-based clinical guideline even more pressing since clinicians may only be confronted with a few cases throughout their careers. For the establishment of such guidelines, more randomized controlled trials are needed to improve the level of supporting evidence. In the research, the importance of increased awareness of the disease entities and the possibility of an autoimmune etiology in cases of treatment-refractory seizures have also become apparent, since early treatment initiation is impossible without recognition of the cause.

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APPENDIX

Attachment 1: Modified Rankin Score

mRS score	Description
0	No symptoms at all
1	No signifcant disability despite symptoms; able to carry out all usual duties and activites
2	Slight disability; unable to carry out all previous activiites byt able to look after own affairs without assitance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Attachment 2: Cognitive performance scale

CPS	Description
0	Intact
1	Borderline intact
2	Mild impairment
3	Moderate impairment
4	Moderately severe impairment
5	Severe impairment
6	Very severe impairment